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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/670,128	09/26/2000	E. Premkumar Reddy	6056-251-CT1	5662

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EXAMINER	
NICKOL, GARY B	
ART UNIT	**PAPER NUMBER**
1642	13

DATE MAILED: 10/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/670,128	REDDY ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-12,14 and 17-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

The Amendment filed July 30, 2002 (Paper No. 12) in response to the Office Action of February 26, 2002 is acknowledged and has been entered.

Claims 1-29 are pending.

Claims 1-12, 14, and 17-29 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claim 13 was amended.

Claims 13, and 15-16 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

New Rejection:

Claims 13, 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garcia *et al.* (Cell Growth & Differentiation, Vol.8, pages 1267-1276, December 1997, IDS) and Takemoto *et al.* (Proc.Natl.Acad.Sci., Vol. 94, December 1997, pages 13897-13902) as further evidenced by (Univ. Mich Med. School, Proc. Ann. Meet. Assoc. Cancer Res., 1997, 38, A3725, meeting abstract).

The claims are drawn to a method for determining the metastatic potential of a cancer in an afflicted patient comprising obtaining a sample of tumor tissue from the patient, obtaining a sample of normal tissue from the patient; determining the level of activated STAT-3 protein in

the sample of tumor tissue and in the sample of normal tissue from the patient, wherein an increased level of activated STAT-3 protein in the tumor tissue as compared to the control tissue indicates an increased metastatic potential of said tumor (Claim 13); wherein determining the level of activated STAT-3 protein comprises determining the relative level of phosphorylated STAT 3 protein (Claim 14); wherein the level of phosphorylated STAT-3 protein is determined by contacting the sample with an antibody which binds said phosphorylated protein (Claim 15).

1. Garcia *et al.* teach that elevated STAT3 activity was present in five of nine breast carcinoma cell lines examined but not in any of three cell lines derived from normal breast epithelial tissue (page 1271, 1st column). Garcia's methods employed determining the relative level of phosphorylated STAT 3 protein by contacting the samples with an antibody which binds the phosphorylated protein (see Figure 8, Lane C). Garcia *et al.* further teach that studies of "primary tumors" indicate that elevated STAT3 activation also occurs in human breast tumors compared to adjacent normal tissue (page 1274, 1st column, 1st paragraph) and that, overall, constitutive activation of Stat3 is a frequent event in breast carcinoma cells.
2. Garcia *et al.* do not teach patient sampling of STAT3 as an indicator of the metastatic potential.
3. Takemoto *et al.* sample activated STAT3 proteins from cancer patients (Figure 2, page 13900) and further report that that the "cells of three patients, whose extracts revealed constitutive activation of STAT proteins, actively synthesized DNA, whereas in the case of patient 2, the absence of STAT activation was consistent with a much lower percentage of cells in S phase and 94% of cells arrested in G_0/G_1." (page 13900, last

sentence). Takemoto *et al.* further substantiate the current literature regarding STATs in that constitutive activation of STATs has been correlated with cell transformation (page 13901, 2nd column, 4th paragraph).

4. The Univ. of Michigan Medical school report high levels of constitutively activated STAT-3 in tissue cells derived from both primary and metastatic breast tumor specimens.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to modulate the method of Garcia *et al.* so as to sample STAT3 protein from a patient "afflicted" with breast cancer (and compare it to normal tissue) in order to determine the metastatic potential of the cancer. One would have been motivated to do so because Garcia *et al.* teach that studies of "primary tumors" indicate that elevated STAT3 activation occurs in human breast tumors compared to adjacent normal tissue and that, overall, constitutive activation of Stat3 is a frequent event in breast carcinoma cells. Moreover, from direct assays of cancer patients, Takemoto *et al.* clearly teach that constitutive activation of Stat3 is also consistent with increased DNA synthesis and that constitutive activation of STATs has been correlated with cell transformation. And, as further evidenced by the Univ. of Michagan Medical School, STAT-3 is constitutively activated in both primary and metastatic breast tumors. Taken together, the combination of the references clearly suggest to one of ordinary skill in the art a reasonable expectation of success of determining the metatastic potential of a cancer in an afflicted patient comprising determining the level of activated STAT-3 protein in a sample of tumor tissue wherein an increased level of activate STAT-3 protein indicates an increase metastatic potential.

Applicants argue that it was improper to reject the claims under 35 USC 112, 2nd paragraph as vague and indefinite while also rejecting the claims as obvious (page 4) since a finding of obviousness requires a reliance on speculative assumptions as to the meaning of the claims. Applicants argue that the Examiner is required to set forth the interpretation of the allegedly indefinite phrase that was used in applying the prior art rejection. This argument has been considered and is found persuasive. The Examiner apologizes for the oversight. And, in further view of applicant's arguments (Paper No. 12, pages 3-4) regarding the meaning of "metastatic potential", the rejections under 35 USC 112, 2nd paragraph (Paper No. 10, page 3-4) are withdrawn.

Turning to applicant's arguments regarding the 103(a) rejection in Paper No. 10, pages 4-6, it should be noted that this is a new rejection because new art has been added. (The previous rejection only contained the prior art of Garcia *et al.* and Takemoto *et al.*).

Applicant's argue (page 5) that Garcia does not coorelate the activation of STAT-3 with the ability of the cells to metastasize, but rather characterizes STAT-3 activation as an early event in Src-induced oncogenic transformation. This argument has been considered but is not found persuasive. The characterization of STAT-3 activation as an "early event" does not limit the cancer cells from their ability or *potential* to metastasize. In fact, Garcia *et al.* teach that activation of c-Src and EGFR kinases is associated with malignant progression of human breast cancer (page 1271, 1st column, 2nd paragraph). And "malignant progression" of cancer cells is a determinant of the potential of cancer cells to metastasize. In contrast, applicants have further argued (page 7) that evidence that a gene or molecular marker is involved in tumorigenesis does not necessarily mean that the gene or marker is relevant to the metastatic potential of the cell.

This argument has been considered but is not found persuasive. In common to the teachings of Garcia *et al.* and Takemoto, the Univ. of Mich. Medical School article demonstrated that both primary and metastatic tumor specimens expressed high levels of constitutively activated STAT3. Thus, even assuming that Garcia characterizes STAT-3 as an early event, such teachings do not limit one of ordinary skill in the art from determining whether or not cancer cells have the potential to metastasize, because such an event, such as the constitutive activation of STAT-3, is continuous. In other words, it does not appear that STAT-3 activation is halted at the beginning of the oncogenic transformation since STAT-3 has also been found to be activated in metastatic tissue. Applicant's further argue (page 6) that Takemoto does not correlate STAT-3 activation with metastatic potential, but rather discusses STAT-3 activation only in terms of cellular transformation. This argument has been considered but is not found persuasive. The teachings of Takemoto are used in combination with the teachings of Garcia *et al.* and the Univ. of Michigan to show success in "cancer patient" sampling of activated STAT-3. In this case, it appears that Applicant has argued and discussed the reference individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981). Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention

must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

All other rejections and or objections are withdrawn in view of applicant's amendments and arguments there to.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
October 21, 2002